Excerpts from

THE PLACENTA: TO KNOW ME TO IS LOVE ME

Gestational Trophoblastic Disease: Hydatidiform Mole

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Gestational Trophoblastic Disease (GTD) includes *hydatidiform mole, invasive mole, placental site trophoblastic tumor* and *choriocarcinoma*, a spectrum of tumors and tumor-like conditions associated with pregnancy, characterized by proliferation of pregnancy associated trophoblastic tissue of progressive malignant potential. These lesions arise from trophoblastic cells which persist after incomplete evacuation of a hydatidiform mole, abortus or placenta in response to some type of carcinogenic "trigger." ***Hydatidiform mole is*** an abnormal placenta which develops after abnormal fertilization and is characterized by hydropic chorionic villous swelling and trophoblastic proliferation.

Hydatidiform moles are androgenic. That is, they are derived exclusively *from palernal* chromosomes because a single sperm fertilizes an ovum devoid of maternal chromosomes with subsequent duplication of the sperm complement of chromosomes to 46,XX (46,YY is lethal), a diploid, ***complete hydatidiform mole (CHM)***. CHM may also develop when two sperm fertilize an "empty" ovum, with subsequent duplication of the chromosome complement of both sperm to tetraploid zygotes 92, XXXX or 92, XXYY.

A ***partial hydatidiform mole (PHM)*** develops when a normal egg (i.e., with its normal complement of maternal chromosomes) receives a double complement of paternal chromosome (either from 2 sperm or from 1 sperm which has duplicated) to form triploid zygotes 69,XXY, 69,XXX, 69,XYY.

Molar transformation of the conceptus is believed to result from concentration of the 4-5 lethal genes typically present in the heterozygous state. Such molar transformation includes excessive villous edema with gross nodular and microscopic swelling culminating in cyst formation, disintegration of blood vessels and, variable trophoblast proliferation.

CHM ranges from 0.3-2.0 cm diameter, grape-like, transparent vesicle, without identifiable gestational sac, amnion, umbilical cord nor fetal tissue. Microscopically, the villi are edematous, lack blood vessels and have cistern-like cavities. They are connected to each other by thin strands of connective tissue, the remnants of the former main stem villi. Variable degrees of proliferation, pleomorphism and anaplasia are present, involving syncytiotrophoblasts, cytotrophoblasts and extravillous trophoblasts. The abnormal trophoblast proliferation is haphazard and circumferential around the villus, in contrast to the normal "polar" proliferation of the normal, early placenta.

PHM consists of otherwise normal immature placental tissue admixed with occasional molar transformed vesicles, often with an identifiable gestational sac with amnion, cord or embryo/fetus. Microscopically, the PHM is a mixture of small, fibrotic "normal" villi and large, irregular hydropic villi with multifocal mild to moderate trophoblast hyperplasia (predominantly syncytiotrophoblast); cisterns may be present but are less prominent. When fetal tissue is found, malformations are often present, particularly syndactyly, a feature common to triploid fetuses.

Clinical Course. Maternal age is the most important risk factor for hydatidiform mole, seen more commonly in women under 20 and over 45 years of age, especially those with a history of molar pregnancy. There is a wide frequency of variation between different races; Hawaiian, Philippine and Japanese women have the highest incidence (up to 1:500 pregnancies) compared to 1:1500 pregnancies in the United States. Moles recur in 0.6-2.6% of subsequent pregnancies, especially in women with a history of multiple spontaneous abortions. Recurrent moles may be more malignant, requiring treatment for residual disease.

Molar tissue may embolize to the lung spontaneously or during evacuation, causing acute pulmonary hypertension, edema, disseminated intravascular coagulation and even death. "Benign" molar tissue may grow in the lungs, hence the term "benign metastasizing mole."

Interestingly, hydatidiform moles have only been reported in humans; no other primate has exhibited this pathology. (See diagram next page.)

	Complete Hydatidiform Mole		Partial Hydatidiform Mole
Incidence in U.S.	1:2000		1:700
Ovum	devoid of maternal chromosomes		normal number of maternal chromosomes
Fertilized by	1 sperm (90%)	or 2 sperm (10%)	1 or 2 sperm
Karyotype	46,XX	92,XXXX or 92,XXYY	69,XXY (70%) 69,XXX (27%) 69,XYY (3%)
Ploidy	diploid	tetraploid	triploid
Embryonic development	none	none	yes, (amnion, cord and/or embryo/ fetus)
Placental molar transformation	complete	complete	partial
POC bulkiness	very bulky: much greater than expected for gestational age, up to size typical of near term pregnancy		less bulky, but still greater than expected for gestational age
Clinical presentation	- late first trimester or early second trimester bleeding - no fetal heart tones -severely elevated bHCG (product of molar villi) -characteristic ultrasound appearance - pregnancy induced hypertension before 24 weeks		- typically unsuspected - presents as missed abortion with late first trimester bleeding
Treatment	- complete evacuation - post evacuation bHCG monitoring (should fall to 0 within 100 days) - if doesn't fall to zero, chemotherapy is typically successful		- complete evacuation
Metastatic potential	yes		no
Persistent gestational trophoblastic tumor	20%: 18% to invasive mole, 2% to choriocarcinoma		5%
Malignant transformation	2%		rare